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Immunopathogenesis of infection with the visceralizing *Leishmania* species

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Abstract

Human leishmaniasis is a spectral disease that includes asymptomatic self-resolving infection, localized skin lesions, and progressive visceral leishmaniasis. With some overlap, visceral and cutaneous leishmaniasis are usually caused by different species of Leishmania.

This review focuses on host responses to infection with the species that cause visceral leishmaniasis, as they contrast with species causing localized cutaneous leishmaniasis. Data from experimental models document significant differences between host responses to organisms causing these diverse syndromes. The visceralizing *Leishmania* spp. cause localized organ-specific immune responses that are important determinants of disease outcome. Both the *Leishmania* species causing cutaneous and those causing visceral leishmaniasis require a Type 1 immune response to undergo cure in mouse models. However, during progressive murine infection with the visceralizing *Leishmania* sp., the Type 1 response is suppressed at least in part by TGF-β and IL-10 without type 2 cytokine production. This contrasts with the cutaneous species *L. major*, in which a Type 2 response suppresses type 1 cytokines and leads to murine disease progression. Population and family studies are beginning to elucidate human genetic determinants predisposing to different outcomes of *Leishmania* infection. These studies should eventually result in a better understanding of the immunopathogenesis and the spectrum of human leishmaniasis.

1. Introduction

The *Leishmania* spp. are a diverse group of organisms belonging to the order *Kinetoplastida* and the family *Trypanosomatidae*. The genus can be divided into two sub-genera, *Leishmania (Leishmania)* spp., and *Leishmania (Viannia)* spp. (Table 1). The visceralizing *Leishmania* spp. belong to the *L. (Leishmania)* sub-genus, and include *L. donovani* and *L. infantum* in the Old World and *L. chagasi* in the New World. Although different in name and geographic origin, molecular data are suggesting that *L. infantum* and *L. chagasi* may actually be one and the same species [1]. *Leishmania donovani* and *L. infantum/chagasi* usually cause disseminated disease in humans, and in turn most cases of visceral leishmaniasis can be attributed to them. However, there is considerable overlap in clinical manifestations caused by the various *Leishmania* spp., and there are reported cases of cutaneous lesions due to *L. chagasi/infantum* and *L donovani* and cases of visceral disease due to *L. amazonensis* [2] and *L. tropica*[3–5].

Infection with the visceralizing *Leishmania* spp. leads to variable manifestations in humans and in experimental rodent hosts. The extent to which the variation in manifestations of disease is caused by genetically defined host versus parasite factors is not settled, but studies have made it clear that there are contributions from both. This review will focus on host responses to infection with *L. donovani* and *L. infantum/chagasi*, and how these differ from responses to species of *Leishmania* that typically cause human cutaneous leishmaniasis (e.g. *L. major*).

Abbreviations: DC, Dendritic cell; IL-2R, Interleukin 2 receptor; LPG, Lipophosphoglycan; MZM, Marginal zone macrophages; PALS, Periarteriolar lymphoid sheath; PBMC, Peripheral blood mononuclear cell; PKDL, Post kala azar dermal leishmaniasis; PPG, Proteophosphoglycans; TGF-β, Transforming growth factor-β.

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Table 1
Major species of *Leishmania* infecting humans [156]

Species[a]	Major disease syndrome	Geographic location
L. (L.) donovani	Visceral leishmaniasis, PKDL[b]	India, North and Eastern China, Pakistan, Nepal
L. (L.) infantum[c]	Visceral leishmaniasis	Mediterranean, Middle East, Balkans, Asia, northwest China, northern and sub-Saharan Africa
L. (L.) chagasi[c]	Visceral leishmaniasis, cutaneous leishmaniasis (rare)	Latin America
L. (L.) archibaldi	Visceral leishmaniasis, cutaneous leishmaniasis	Sudan, Kenya, Ethiopia
L. (L.) major	Cutaneous leishmaniasis	Middle East, northwest China, northwest India, Pakistan, Africa
L. (L.) tropica	Cutaneous leishmaniasis, viscerotropic leishmaniasis	Mediterranean, Middle East, west Asiatic region, India
L. (L.) aethiopica	Cutaneous leishmaniasis, diffuse cutaneous leishmaniasis	Ethiopia, Kenya, Yemen
L. (L.) mexicana	Cutaneous leishmaniasis, rarely mucosal leishmaniasis	Mexico, Central America, Texas
L. (L.) amazonensis	Cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, rarely visceral leishmaniasis	Amazon basin, Brazil
L (L.) pifanoi	Cutaneous leishmaniasis, diffuse cutaneous leishmaniasis	Venezuela
L. (L.) garnhami	Cutaneous leishmaniasis	Venezuela
L. (L.) venezuelensis	Cutaneous leishmaniasis	Venezuela
L. (V.) braziliensis	Cutaneous leishmaniasis, mucosal leishmaniasis	Latin America
L. (V.) guyanensis	Cutaneous leishmaniasis	Guyana, Surinam, Amazon basin
L. (V.) peruviana	Cutaneous leishmaniasis	Peru, Argentina highlands
L. (V.) panamensis	Cutaneous leishmaniasis	Panama, Costa Rica, Colombia

[a] The subspecies *Leishmania Leishmania* or *Leishmania Viannia* are indicated on this table. The subspecies designation is not indicated throughout the text.
[b] PKDL—post-kala-azar dermal leishmaniasis.
[c] Evidence is accumulating that *L. infantum* and *L. chagasi* are the same species.

Finally, much of the literature on experimental cutaneous leishmaniasis focuses on *L. major*, and it is becoming apparent that other cutaneous species, such as *L. amazonensis*, elicit yet distinct host responses [6,7].

2. The Th1/Th2 paradigm: *L. major* models of cutaneous leishmaniasis in mice

Studies of murine models have underscored biological differences between *L. major*, a species that typically causes cutaneous leishmaniasis in humans, and the *Leishmania* spp. that cause visceralizing leishmaniasis. Work of Mossman and Coffman in the 1980s documented distinct subsets of $CD4^+$ T cells including Th1 cells that lead to macrophage activation and B cell secretion of immunoglobulin subtypes (e.g. IgG2a) able to fix complement and neutralize viruses. In contrast, Th2 cells help antibody production of IgG1, IgE and IgA and secrete cytokines that prevent Th1 development [8]. Additional types of $CD4^+$ cells expressing TGF-β and/or IL-10 have more recently been described. These include regulatory T cells that constitutively express the IL-2R subunit CD25, and TGF-β-producing Th3 cells located in the gut. For the purpose of this review we will refer to an immune response that is dominated by IFN-γ as a Type 1 response, and a response characterized by IL-4, IL-13 and/or IL-5 as a Type 2 immune response. An immune response characterized by abundant TGF-β will be called a 'Type 3' response.

The chronic persistent nature of leishmaniasis favors the development of polarized immune responses. Indeed, murine leishmaniasis caused by *L. major* provides an exquisite demonstration that Th1 and Th2 subsets can influence the course of disease toward opposite poles depending on the genetic predisposition of the murine host. Progressive *L. major* infection of susceptible BALB/c mice is promoted by expansion of Th2 cells producing IL-4, IL-10 and IL-13. In contrast, Th1 expansion in resistant mice (e.g. C3H), initiated by IL-12 and IFN-γ, causes *L. major* lesions to resolve [9–11]. Th2 cells lose their IL-12 responsiveness due to decreased expression of the β1 and the β2 subunits of the IL-12 receptor during *L. major* infection [12,13]. An early burst of IL-4 occurs in susceptible BALB/c mice and precedes disease progression [14]. This is caused by expansion of T cells expressing TCR Vα8Vβ4 specific for the *L. major* LACK antigen (homolog of mammalian RACK1) [15,16]. Indeed the response to LACK has been found to dominate the course of *L. major* disease in mice. As such, mice in which Vβ4 expressing cells are deleted with a superantigen become resistant; whereas control mice with deleted Vβ6 remain susceptible, to *L. major* infection [15]. Continuous expression of LACK in mouse tissues render them tolerant to LACK, and this inability to respond to LACK causes these mice to down-regulate their Type 2 response and heal infection [16].

3. Visceralizing *Leishmania* spp. in experimental animal models: tissue-specific immune responses and the lack of a Th1/Th2 dichotomy

Rodent models have been used extensively in the study of *L. donovani* and to a lesser extent *L. chagasi* and *L. infantum*. Mice are either genetically susceptible or resistant to infection, but even susceptible strains heal their infections [17]. Thus, they are better models of self-healing